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The hazard of (sub)therapeutic doses of anticoagulants in non-critically ill patients with Covid-19: the Padua province experience

Running Head : The incidence of bleeding in patients with Covid-19

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ESSENTIALS

° In COVID, information on benefit/risk ratio of (sub)therapeutic doses of anticoagulants is lacking

° We evaluated the rate of bleeding in non-critically ill COVID patients who received anticoagulants

° The rate of bleeding was high in patients treated with (sub)therapeutic doses of anticoagulants

° In the latter, overall mortality did not differ from that of patients treated with prophylactic doses

Abstract 248 words

Background: COVID-19 is responsible for a worldwide pandemic, with a high rate of morbidity and mortality. The increasing evidence of an associated relevant pro-thrombotic coagulopathy has resulted in an increasing use of antithrombotic doses higher than usual in COVID-19 patients. Information on the benefit/risk ratio of this approach is still lacking.

Objective: to assess the incidence of relevant bleeding complications in association with the antithrombotic strategy, and its relationship with the amount of drug.

Methods: Consecutive COVID-19 patients admitted between February and April 2020 were included in a retrospective analysis. Major bleedings (MB) and clinical relevant non-major bleeding (CRNMB) were obtained from patient medical records and were adjudicated by an independent committee.

Results: Of the 324 patients who were recruited, 240 had been treated with prophylactic doses and 84 with higher doses of anticoagulants. The rate of the composite endpoint of MB or CRNMB was 6.9 per 100 person/months in patients who had been given prophylactic doses, and 26.4 per 100 persons/months in those who had been prescribed higher doses (HR 3.89; 95%CI, 1.90 to 7.97). The corresponding rates for overall mortality were 12.2 and 20.1 per 100 person/months, respectively.

Conclusions: The rate of relevant bleeding events were high in patients treated with (sub)therapeutic doses of anticoagulants. In the latter group, overall mortality did not differ from that of patients treated with standard prophylactic doses and was even higher. Our result does not support a strategy of giving (sub)therapeutic doses of anticoagulants in non-critically ill patients with COVID-19.

Keywords: anticoagulants, bleeding, coronavirus 2019, COVID-19; venous thromboembolism

2525 WORDS

INTRODUCTION

COVID-19 (acronym of COronaVIrus Disease 2019), or acute respiratory disease determined by a novel beta coronavirus, named SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus 2) is an infectious respiratory disease, responsible for a worldwide pandemic, with a high rate of morbidity and mortality [1-7]. COVID-19 is characterized by a wide spectrum of clinical manifestations, ranging from no or flu-like syndrome to severe acute respiratory distress syndrome. In current practice, mainly based on the experience gained in China, where the first disease outbreak developed in late 2019, symptomatic patients are treated with pharmacological cocktails including antiviral agents, hydroxychloroquine, macrolides, antiphlogistic and antithrombotic drugs [2,8-15].

The use of antithrombotic agents in COVID-19 hospitalized patients was initially guided by the recommendations issued by several international societies for protection against venous thromboembolism (VTE) in high-risk medical patients [16]. Later on, increasing evidence has shown that a remarkable pro-thrombotic coagulopathy may occur in the clinical course of several COVID-19 patients, leading to the development of fatal and non-fatal venous and arterial complications, even in patients who had been administered prophylactic doses of heparins or fondaparinux [13,17- 28]. This has resulted in an increasing use of antithrombotic doses higher than usual, especially in patients perceived as being at a higher thromboembolic risk because of an unusually high D-dimer value and/or the presence of additional comorbidities [13]. As available information on the benefit/risk profile of this approach is still lacking, we retrieved information from a broad number of consecutive patients with non-critical COVID-19 who had been admitted to two medical wards and had been prescribed variable doses of antithrombotic drugs according to the physicians' perception of the thromboembolic risk. The primary study endpoint was the incidence of relevant bleeding complications occurring in association with the antithrombotic strategy, and its relationship with the amount of drug. We also assessed whether and to what extent factors other than antithrombotic agents can affect the haemorrhagic risk. The choice of the drug was left to the discretion of attending physicians, as was its dosage and duration.

METHODS

Patients

All consecutive patients admitted to two medical wards (the non-intensive COVID-19 Unit of the University Hospital of Padua and the COVID-19 Hospital of the Padua Province, Ospedali Riuniti Padova Sud, Monselice, both in Northern Italy) with laboratory-confirmed SARS-CoV-2 infection between February26th and April 6th 2020 were eligible for this retrospective investigation. According to the WHO laboratory guidelines, confirmation for SARS-CoV-2 was defined as a positive result of real-time reverse transcriptase-polymerase chain reaction assay of nasal and pharyngeal swabs [1]. Patients with critical disease (i.e., patients requiring intubation for ventilatory support or intensive care) were excluded, as were those who could not receive antithrombotic prophylaxis and those on indefinite treatment with vitamin K antagonists or direct oral anticoagulants (DOAC) for cardiovascular disorders. The investigation was conducted according to the principles expressed in the Declaration of Helsinki (2001) and local regulations. The study protocol was approved by the cardiovascular section in-house Ethics Committee on Human Research of the Padua Province.

Data collection

Study data and clinical information were collected and managed by medical staff using REDCap electronic data capture tools hosted at the University of Padua. For each patient, the following baseline data were collected: age, sex, body mass index (BMI), D-Dimer, history of previous VTE or bleeding, the Padua Prediction Score (PPS) and several bleeding risk factors (indicated in Table 1). In addition, the main pharmacologic treatments other than antithrombotic drugs were recorded, as was the need for subsequent intensive care.

Study groups

The choice of the antithrombotic agent was left to the discretion of attending physicians, who decided to use prophylactic or higher doses based on the perceived thromboembolic risk, in turn guided by the value of baseline D-dimer and/or the presence of comorbidities, such as obesity, cancer, venous insufficiency, personal or familiar history of VTE, known thrombophilia or ongoing treatment with hormonal or antipsychotic drugs. From the clinical charts we retrieved information on each of the three antithrombotic drugs that had been administered (unfractionated heparin, enoxaparin or fondaparinux), and predefined the dose intensity as being prophylactic or higher. Daily doses of unfractionated heparin up to 15,000 U, of enoxaparin up to 4000 U and of fondaparinux up to 2.5 mg were labelled as prophylactic (prophylaxis group). Higher daily doses, usually adjusted to body weight or laboratory parameters, were aggregated in one group [(sub)therapeutic group] regardless of the drug amount.

Study outcomes

The primary endpoint was the composite of major bleeding (MB) and clinically relevant non-major bleeding (CRNMB) occurring in each of the two study groups during the administration of antithrombotic agents (up to two days after their discontinuation). Secondary outcomes were the single components of the primary one, as were objectively confirmed symptomatic VTE and all-cause mortality. The severity of bleeding was defined according to the scientific and standardization committee of the International Society on Thrombosis and Haemostasis [29]. An independent committee, unaware of the patients' clinical details reviewed and adjudicated all bleeding events. For the confirmation of lower extremities DVT and PE, leg vein ultrasonography and CT angiography were used, respectively, with the adoption of widely accepted diagnostic criteria.

Statistical analysis

The time to the primary outcome of MB or CRNMB was calculated as the time from hospitalization to the event occurred or to death or VTE for those patients who experienced these events during the 30 days of hospitalization or 30 days for the survivors. Death and VTE were considered competing events. The rate of the primary composite outcome was estimated with 95% confidence intervals (CI) calculated with the Poisson method. Potential predictors of the primary outcome were tested in a univariate Cox regression model for competing hazards using the Fine and Grey method and those found to be statistically significant at the 10% level were included in a multivariable Cox regression model with stepwise backward selection. Potential predictors of death for any cause were tested in a univariate Cox regression model, and those found to be statistically significant at the 10% level were included in a multivariable Cox regression model with stepwise backward selection. Results are presented as p-values and hazard ratios with 95% confidence intervals. All the statistical tests were two-tailed and conducted at a significance level of 5% if not otherwise stated and the analyses were performed with SAS 9.4 (SAS Institute Inc., Cary, NC, USA) for Windows.

RESULTS

Patients and study groups

Overall, we retrieved data from 448 eligible patients with non-critically ill COVID-19. Of them, 23 were excluded because of the need for intensive care or ventilatory support at the time of admission, 53 because of indefinite treatment with vitamin K antagonists or novel anticoagulants, and 48 because of lack of antithrombotic prophylaxis. Accordingly, 324 patients were recruited for the current investigation. The median age was 71 years (IQR 59-82) years and 181 were men (55.9%). In all patients, radiologic and thoracic ultrasound findings of COVID-19 were found.

Of the 324 patients, 240 had been treated with prophylactic doses of anticoagulants (1 with UFH, 193 with LMWH and 45 with fondaparinux); and the remaining 84 with ~~higher doses~~ (sub)therapeutic doses (78 with LMWH and 6 with fondaparinux). More details about higher doses are displayed in table 1.

At variable time during hospitalization, 30 patients (9.3%) required intensive care for a median length of stay in ICU of 11 days (IQR 6-17): 7 (2.9%) in the prophylaxis group and the remaining 23 (27.4%) in the treatment group. Table 1 summarizes the main baseline and clinical characteristics of the study cohort, separately for each group.

Study outcomes

Table 2 details the primary and secondary events occurring in our cohort, separately in each of the two study groups. During anticoagulation, the primary end-point developed in 15 patients who had been given prophylactic doses (11 receiving LMWH and 4 fondaparinux), corresponding to an incidence rate of 6.9 per 100 person/months (95%CI, 3.9 to 11.5; 8 MB and 7 CRNMB), and in 18 patients who had been prescribed (sub)therapeutic doses (LMWH and fondaparinux in 17 and one, respectively), corresponding to an incidence rate of 26.4 per 100 person/months (95%CI; 15.6 to 41.6; 8 MB and 10 CRNMB). Two fatal bleeding events developed in patients who had received prophylactic doses (0.9 per 100 person/months) and two in patients who had been prescribed higher doses (2.9 per 100 person/months).

VTE developed in six patients who had been given prophylactic doses and in three patients who had been prescribed higher doses. Death from any cause was reported in 27 patients who had been given prophylactic doses, corresponding to an incidence rate of 12.2 per 100 person/months (95% CI, 8.1 to 17.8) and in 14 patients who had been prescribed higher doses, corresponding to an incidence rate of 20.1 per 100 person/months (95% CI, 11.0 to 33.8). Age > 80 years, high PPS, COVID phenotype, and moderate-to-severe renal impairment were found to be independent predictors of all-cause mortality (table 3).

Predictors of the primary endpoint

In the multivariable Cox regression model, use of (sub)therapeutic doses of anticoagulants (HR 3.89; 95% CI, 1.90 to 7.97; p=<.001), age older than 80 years (HR 3.40; 95% CI, 1.51 to 7.65; p=0.003) and concomitant dual antiplatelet therapy (HR 9.4; 95% CI 2.6 to 33.7; p< .001) were found to be independent predictors of major or clinically relevant non-major bleeding (table 4).

DISCUSSION

The increasing awareness that low-dose anticoagulants may be ineffective for prevention of thrombotic complications in the course of COVID-19, including the development of micro-thrombosis in the lung vessels, has induced several clinicians to consider the use of sub-therapeutic or even therapeutic doses of antithrombotic agents in all admitted patients, challenging their hemorrhagic potential [13,30]. The results of our retrospective cohort study do not support this strategy. Indeed, the rate of symptomatic complications occurring during the clinical course of patients who received (sub)therapeutic doses of heparins or fondaparinux did not differ from that of patients given conventional preventive doses, nor did the rate of overall mortality, which was even higher in the former group, most likely because of the recruitment of patients who were on average older and had a higher thromboembolic risk. By converse, the rate of clinically relevant bleeding complications among patients allocated to (sub)therapeutic doses exceeded by far that recorded among those treated with preventive doses. Based on the results of our multivariate proportional hazards regression model, the anticoagulant dose was the strongest determinant of the bleeding risk. As the benefit/risk ratio of high-dose anticoagulants is in striking contrast with that expected in the treatment of most patients with acute vascular disorders [31], our results suggest that thrombotic complications are unlikely to play a key role in determining the prognosis of COVID-19.

Although obtained with a retrospective study, our results are robust. We recruited two large cohorts of consecutive patients who were admitted to medical wards. In addition, predefined criteria were used for the adjudication of the primary endpoint. Finally, because of the general difficulty in interpreting the cause of death we decided to include all-cause mortality among the (secondary) end-points, in such a way accepting the risk of diluting the contributing role of PE to the patients' mortality but obviating that of missing deaths imputable to pulmonary embolism or thrombosis.

Not surprisingly, the incidence of major or clinically relevant bleeding complications occurring during hospitalization was remarkably higher in patients treated with (sub)therapeutic than in those receiving preventive doses of antithrombotic drugs. Of interest, in each of the two study cohorts the observed incidence was consistent with that expected in the respective field [16, 31]. As (sub)-therapeutic doses of antithrombotic drugs failed to reduce the risk of fatal or non-fatal thrombotic complications while simultaneously increasing the haemorrhagic risk, their use in patients with non-critically ill COVID-19 should be discouraged. Our results are consistent with those of a recent multicentre retrospective American study [33].

Among the potential study limitations are the lack of a standardized approach for the detection of VTE disorders and the heterogeneous distribution of baseline parameters between the two study groups.

Unusually crowded wards and inherent risks of contagion dissemination led attending physicians to modify the diagnostic workup for suspected VTE, limiting the ultrasound detection of DVT only to patients with unexplained leg oedema and CT pulmonary angiography only to those with inexplicable worsening of their respiratory symptoms.

This can account for the discrepancy between our findings and those of recent studies where the occurrence of VTE complications was instead more extensively investigated [20, 32]. In our study cohort, both patients treated with prophylactic and those treated with higher dose of anticoagulants had low median plasma levels of D-dimer (255 and 270 ug/L, respectively).Levels higher than 1000 ug/L were found only in 11% of cases. Of interest, in these patients, the risk of bleeding, VTE and death was not influenced by the anticoagulant dose (data not reported). According to the results of Tang et al. [13] on patients with severe COVID-19, prophylactic doses of heparin reduced mortality compared with no treatment only in patients with D-dimer levels higher than 3000 ug/L, while no effect was observed in those with lower levels. Therefore, use of (sub)therapeutic doses in patients with less severe Covid-19 and lower D-dimer levels is unlikely to be beneficial while increasing the bleeding risk.

The discrepancy in the baseline laboratory and clinical parameters between the two groups is, in turn, dependent on the arbitrary selection of anticoagulant doses. In fact, the decision was left to attending physicians, who generally prescribed the (sub)therapeutic doses to patients perceived as being at a higher thromboembolic risk. Not surprisingly, therefore (as shown in Table 1), patients belonging to the latter group were on average older, had a higher PPS and a longer hospital stay, and more often needed intensive care. Because of these unavoidable limitations, we decided not to include the rate of VTE complications and that of death among the primary study endpoints. By contrast, the primary safety outcomes (major and clinically relevant non-major bleeding) were accurately recorded and classified and were independently reviewed. As a result of our multivariate proportional hazards regression model, the dose of antithrombotic agents was the main contributor to the remarkable excess in the bleeding risk observed among patients receiving high doses of the antithrombotic drug over those assigned low preventive doses.

Of interest, among the five patients treated with concomitant dual antiplatelet therapy, two developed a clinically relevant bleeding (one major bleeding in a patient treated with enoxaparin prophylactic dose and one CRNMB in a patient treated with weight-adjusted dose). Not surprisingly, the administration of dual or triple antithrombotic therapies can significantly increase the risk of bleeding in patients with COVID-19.

In conclusion, the results of our study do not support the currently adopted strategy of giving weight- adjusted doses of anticoagulants in non-critically ill patients with COVID-19 in the absence of thromboembolic complications. They are likely to be dangerous and ineffective. Anyway, we acknowledge that, because of the retrospective design of our study and of its limitations, our results may not be strong enough to allow definitive conclusions. Furthermore, as for the current investigation we recruited only non-critically ill patients, our conclusions may not apply to more severe patients. The results of prospective randomized studies, including severe patients, are warranted.

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ADDENDUM:

Author contributions:

Study concept and design: R. Pesavento and D. Ceccato;

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Critical revision of the manuscript for important intellectual content: all authors; Statistical analysis: A.C. Frigo, R. Pesavento;

Administrative, technical or material support: R. Pesavento and P. Prandoni;

Study supervision: R. Pesavento, G.Pasquetto, D.Ceccato and M.G. Marchese

R. Pesavento had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

DECLARATION OF CONFLICTING INTERESTS

The authors declare that there is no conflict of interest

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Table 1. Baseline and clinical characteristics of patients who had been given prophylaxis and non-prophylaxis doses of anticoagulants

	prophylactic dose (N=240)	(sub)therapeutic dose (N=84)		prophylactic dose (N=240)	(sub)therapeutic dose (N=84)
Age, years; median, (IQR)	70 (57-81)	77(62-86)	**Type of anticoagulant administered**		
Sex, males	130 (54.2)	51 (60.7)	UFH	1 (0.4)	0
Obesity (N=213)	37 (15.4)	12 (14.3)	LMWH	193 (80.8)	78 (92.9)
Previous VTE	10 (4.2)	7 (8.3)	Fondaparinux	45 (18.8)	6 (7.1)
COVID-pneumonia severity at admission			**Dose of anticoagulant administered**		
Need of low-flow oxygen	177 (73.8)	62 (73.8)	UFH 5000 U TID	1	0
Need of reservoir-mask	51 (21.3)	18 (21.4)	LMWH 40 mg OD	193	0
Need of high-flow oxygen	12 (5.0)	4 (4.8)	LMWH 1mg/Kg BID	0	71
In- hospital stay duration, days, median, (IQR)	12 (8-18)	17 (11-30)	LMWH 0,5 mg/Kg BID	0	7
Need of subsequent ICU care	7 (2.9)	23 (27.4)	Fondaparinux 2,5 mg	45	0
ICU stay duration, days, median, (IQR)	10 (4-12)	12 (7-18)	Fondaparinux 7,5 mg	0	6
PPS ≥ 4	103 (42.9)	56 (66.7)	Lab-adjusted doses	0	0
D-dimer, ug/L; median, (IQR) (N=281)	252 (155-501)	270 (154-759)	LMWH daily dose, mg, median (IQR)	-	120 (80-140)
			LMWH daily dose, mg, min-max	-	40-200
Bleeding risk factors			**Type of antiplatelet therapy administered**		
e-GFR ≥ 60 ml/min/1.73 m^2	183 (76.3)	53 (63.1)	None	186 (77.5)	66 (78.6)
e-GFR 30-59 ml/min/1.73 m^2	44 (18.3)	24 (28.6)	SAPT	50 (20.8)	17 (20.2)
e-GFR < 30 ml/min/1.73 m^2	13 (5.4)	7 (8.3)	DAPT	4 (1.7)	1 (1.2)
Acute liver failure	9 (3.8)	0	**COVID-specific treatments**		
Bleeding History	9 (3.8)	1 (1.2)	Ritonavir/lopinavir	42 (17.5)	21 (25.0)

Uncontrolled Hypertension	55 (22.9)	14 (16.7)	Hydroxychloroquine	180 (75.0)	71 (84.5)
Chronic blood diseases	5 (2.1)	3 (3.6)	Tocilizumab	6 (2.5)	14 (16.7)
Alcohol abuse	2 (0.8)	0	Remdesivir	1 (0.4)	2 (2.4)
Thrombocytopenia (< 50 x 10^9/L)	3 (1.3)	1 (1.2)	Antibiotics	170 (70.8)	57 (67.9)
GI cancer	1 (0.4)	1 (1.2)	Steroids	77 (32.1)	27 (32.1)
			PPI	154 (64.2)	68 (81.0)

*Values are expressed as number and percentage in round brackets unless is otherwise indicated.

IQR: Interquartile range; ICU: Intensive Care Unit; PPS: Padua Prediction Score; e-GFR: Glomerular filtrate rate (CKD-EPI); GI: Gastrointestinal; UFH: unfractionated heparin; LMWH: Low Molecular Weight Heparin; SAPT: Single Antiplatelet Therapy; DAPT: Dual Antiplatelet Therapy; PPI: Proton-Pump Inhibitor

Table 2. Incidence rate of the outcomes

	Prophylactic dose (N=240)		(sub)therapeutic dose (N=84)	
	N	**Rate***	**N**	**Rate***
**Primary endpoint ** **	15	6.9 (3.9—11.5)	18	26.4 (15.6-41.7)
MB	8	3.7 (1.6 -7.3)	8	11.7 (5.1-23.1)
CRNMB	7	3.2 (1.3-6.7)	10	14.6 (7.0-26.9)
Fatal Bleeding	2	0.9 (0.1-3.3)	2	2.9 (0.3-10.6)
VTE	6	2.8 (1.0-6.0)	3	4.4 (0.9-12.8)
Death for any cause	27	12.2 (8.1-17.8)	14	20.1(11.0-33.8)
Type of MB event				
Intracranial	1	-	0	-
Retroperitoneal	3	-	3	-
Gastrointestinal	3	-	3	-
Intrauterine	1	-	0	-
Muscles	0	-	2	-
Type of VTE event				
Pulmonary embolism	1	-	0	-
DVT in lower limbs	2	-	2	-
DVT in other sites	3	-	1	-

***per 100 person-months (95%CI)**

****MB and/or CRNMB; MB: major bleeding; CRNMB: Clinical relevant Non-Major Bleeding;

VTE: Venous Thromboembolism

Table 3. Characteristics of the study patients by mortality and results of the multivariate Cox regression analysis.

	Death for any cause		
	HR	**95%CI**	**p**
PPS ≥ 4	2.59	1.16-5.78	0.02
Age> 80 years	2.87	1.36-6.03	0.005
COVID phenotype 2	2.78	1.48-5.23	0.001
eGFR 30-59 ml/min/1,73m^2	3.01	1.40-6.48	0.005
eGFR < 30 ml/min/1,73m^2	6.61	2.77-15.74	<.001

Age, gender, PPS, eGFR, COVID phenotype, antiplatelet, antibiotic, steroid and PPI treatment were included in the multivariate regression model.

PPS: Padua Prediction Score; eGFR: estimated Glomerular Filtrate Rate

Table 4. Characteristics of the study patients by bleeding complications and results of the multivariate Cox regression analysis for competitive risks.

	Primary endpoint*		
	HR	95%CI	p
AC (sub)therapeutic doses	3.89	1.90-7.97	<.001
Age> 80 years	3.40	1.51-7.65	0.003
SAPT	0.68	0.24-1.93	0.47
DAPT	9.4	2.6-33.7	<.001

*MB and/or CRNMB; age, eGFR < 30 ml/min/1,73m2, eGFR 30-59 ml/min/1,73m2, eGFR ≥ 60 ml/min/1,73m, 2D-dimer, history of VTE and concomitant antiplatelet therapy were included in the multivariate regression model.AC: anticoagulants; MB: major bleeding; CRNMB: Clinical relevant Non-Major Bleeding; AC: anticoagulants eGFR: estimated Glomerular Filtrate Rate SAPT: single drug antiplatelet therapy; DAPT: dual drug antiplatelet therapy